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Worldwide Literature Alert

Novel Combination Therapy for Intraocular Pressure: Achieving Greater Efficacy and Patient Satisfaction

Based on: Lanzl I, Raber T. Efficacy and tolerability of the fixed combination of brinzolamide 1% and timolol 0.5% in daily practice. *Clin Ophthalmol* 2011;5:291-8.

Fixed-dose combination therapies for elevated intraocular pressure (IOP), which are needed for the large proportion of individuals inadequately controlled on a single agent, have been available for more than 10 years. All of the current fixed-dose combinations include timolol, leaving the second agent to largely define differences in clinical effect. In phase IV data generated with the most recent of these fixed-dose combinations, highly significant objective improvements in IOP control and large subjective differences in favourable assessments were documented after patients were transitioned to the newer combination from those previously available. The ratio of preference for the newer combination over the previous therapy was almost tenfold greater. The 14,000-patient study, conducted in the context of usual care, appears to establish the most recent combination as a benchmark for IOP control because of the concomitant advantages for both efficacy and tolerability.

Finding the Optimal Combination for Efficacy and Tolerability

Most individuals with elevated intraocular pressure (IOP) fail to achieve adequate control on a single agent. Over the past decade, the effort to incorporate 2 agents with different mechanisms of action into a single fixed combination has improved opportunities for efficacy, but individualization of drug choice has been required to achieve adequate efficacy in the context of acceptable tolerability. The most recently developed combination, brinzolamide 1.0% and timolol 0.5%, appears to provide a benchmark due to high levels of patient satisfaction concomitant with reliable efficacy across subgroups.

The tolerability of the brinzolamide/timolol (BT) combination, which generated statistically significant reductions in IOP relative to the previous therapy, was characterized as "overwhelmingly positive" in the recently published phase IV study. Almost 90% of the 14,025 patients evaluated labelled the tolerability as "good" or "very good." The proportion of patients who declared themselves satisfied with treatment was 93.4%, which is an uncommon result from a large study conducted in IOP. These results along with the IOP pressure reductions associated with therapy over the course of the study are particularly compelling because the data from phase IV studies are conducted in the setting of routine patient management.

Real-world Data from Clinical Practice

In the real-world setting of the current study, BT produced better IOP control than all previous therapies analyzed, according to study authors. This efficacy in the context of the high rates of tolerability was identified as the source of the "strong patient preference" expressed by the study population for the newer combination relative to their previous treatment.

This open-label, multicentre phase IV study conducted in Germany sought to determine whether the efficacy and safety of the combination extended to large patient populations participating in usual care. Patients were enrolled at 1161 centres. All decisions regarding switching patients from their current IOP therapy to BT were made by the treating physician. IOP was measured at baseline prior to the switch and again 4 to 6 weeks after. In addition to IOP, standardized data collection sheets captured age, glaucoma type and reason for switch. Patients were asked to assess the tolerability of their previous and new regimens with standardized terms.

The mean IOP at the baseline measure on previous therapy was 20.7 mm Hg. After 4 to 6 weeks of therapy, the mean IOP had dropped to 16.8 mm Hg, a mean decrease of 18.8% ($P<0.0001$). While the largest relative reductions were observed in patients who had switched from single agents to combination BT, there was a consistent reduction from baseline across all previous therapies including other fixed-dose combinations. For example, the mean IOP among patients on brimonidine 0.2%/timolol 0.5% fell from 20.1 mm Hg to 17.4 mm Hg and from 18.5 mm Hg to 16.5 mm Hg for those on dorzolamide 2%/timolol 0.5% after the transition. Importantly, after transition to BT, patient-reported tolerability rose from 32.1% to 86.5% and from 29.2% to 88.9%, respectively.

Study authors reported the magnitude of the change in mean IOP reduction from baseline to the week-4-to-6 visit as 1.9 mm Hg, 2.7 mm Hg and 4.8 mm Hg for those patients previously on a prostaglandin analog (PGA) plus dorzolamide/timolol (DT), brimonidine/timolol or timolol alone who transitioned to BT, respectively. Mean IOP change was also assessed for patients previously on a PGA with either brinzolamide, dorzolamide or DT switched to a PGA + BT (Figure 1).

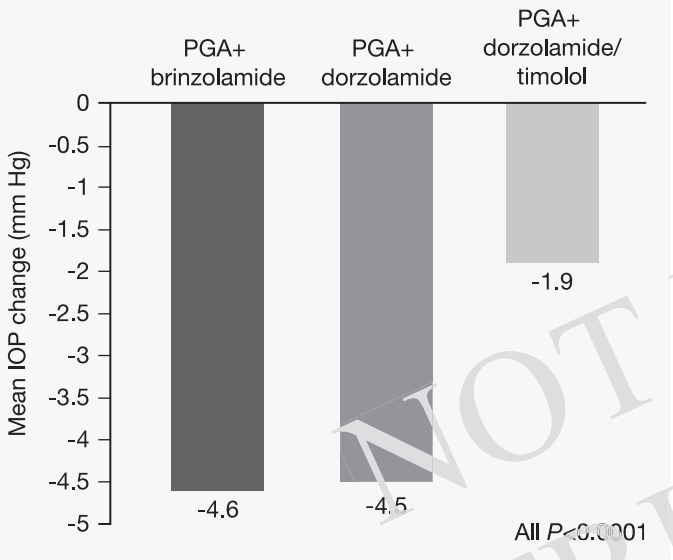
While the authors acknowledged that an open-label study of this type lacks the rigorous controls of a blinded trial, its strengths not only include the very large numbers but also the entry of an unrestricted population receiving therapy under usual circumstances. This setting provided an opportunity to "reveal the efficacy and safety of a drug as it is truly used in clinical practice."

Continued

Summary

Fixed-dosed combinations, all containing timolol, have been developed to improve control of IOP. The strength of these combinations lies in their ability to achieve lower IOP levels with a minimum of adverse events and a maximum of patient comfort. Notably, in this observational study, BT as the most recent of these combinations was preferred by patients when they were switched from their previous single or combination therapy. It is likely that the preference was generated by greater relative efficacy in IOP reductions with a low rate of adverse events.

Figure 1. **Subgroup Change in Mean IOP from Baseline After 4 to 6 Weeks**



Adapted from Lanzl I, Raber T. *Clin Ophthalmol* 2011;5:291-8.

Questions and Answers

This question-and-answer session was conducted with Prof. Ines Lanzl, Department of Ophthalmology, Technical University, Munich, Germany.

Q: Do you feel that the proportion of people switched to BT in this study (60% for tolerability issues and 30% for efficacy issues) is representative of a real-world experience for clinicians?

A: The main overall reason for switching to [this combination] was efficacy (54%). As the study was designed as a non-interventional study, this represents the real-world situation of general ophthalmology practices in Germany. Fixed combinations are especially prescribed if you need more efficacy to lower IOP levels in your patients. This is true also for the fixed combinations of a carbonic anhydrase inhibitor (CAI) and timolol. The situation has been different in the subgroup of switches from DT to BT. Here you have 60% tolerability and 30% efficacy issues as you mentioned in your question. The reason for this may be the different formulation of both drugs. As the pH of DT is about 5.7 and 7.2 for BT, you see more burning and stinging sensations in DT patients than in BT patients (as have been already shown in other clinical studies).

Q: Would this distribution be similar for patients switching after a single vs. a combination IOP-lowering agent?

A: I suppose the distribution would be at least slightly different if you focus on switches from combination therapies. Here you may see less efficacy reasons but more tolerability and/or compliance reasons. But we did not analyze that in this study.

Q: Even though most patients switched to BT because of tolerability concerns, this fixed-dose combination demonstrated greater efficacy on average than all previous therapies. Is this surprising?

A: Of course, you will usually see improved efficacy if you switch from a monotherapy to a fixed combination. Only the group of prostaglandin analogues is generally seen to have a comparable efficacy to the CAI/timolol fixed combination. Nevertheless, we have to keep in mind that in a non-interventional study, physicians tend to include patients who did not reach their target pressure with their previous treatment strategy (often the patients have "baseline" IOPs under previous therapy of about 20 mm Hg). So you might often get better IOP results when switching—which is not always comparable to a clinical study in a parallel group or even crossover design. Nevertheless, such a non-interventional study shows us the options we have and the possible results we might get when switching to a new drug.

Q: The overwhelming patient preference for BT over the previous therapy is supported by improvements in overall treatment satisfaction. Do you think this is a product of tolerability, efficacy, both, or are these difficult to separate?

A: The treatment satisfaction of patients may be mainly explained by the differences in tolerability. Physician satisfaction is usually a combination of efficacy and tolerability/compliance because we need both to get a successful therapy and maintain vision in our patients. □

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Medical Education Network Canada Inc. 132 chemin de l'Anse, Vaudreuil, Quebec J7V 8P3